II. REMARKS

Upon entry of the present amendment, claims 1 to 4 and 7 to 27 will be pending. A marked version showing the amendments to the claims is attached hereto as Exhibit A.

Applicant gratefully acknowledges the Examiner's reconsideration and withdrawal of the species election.

A. Regarding the Amendments

Claims 5 and 6 are cancelled herein without disclaimer, and without prejudice to Applicant pursuing prosecution of subject matter encompassed within the claims as previously pending in an application claiming the benefit of priority of the subject application.

Claims 2 and 21 were amended to refer more specifically to the language of claims 1 and 20, respectively, from which claims 2 and 21 depend. As such, the amendments merely address a formality and do not add new matter.

Claims 1, 12, 18 to 20 and 25 have been amended to more clearly define the target nucleic acids examined according to a method of the invention. The amendments are supported, for example, by previously pending claims 5 and 6, which have been cancelled herein, and at page 1 (Table 1). As such, the amendments are supported by the specification and do not add new matter.

B. Rejections under 35 U.S.C. § 112

The rejections of claims 2, 3 and 21 under 35 U.S.C. § 112, second paragraph, as allegedly vague and indefinite are respectfully traversed.

It is stated in the Office Action that claim 2, which depends from claim 1, is indefinite in reciting "the mutant nucleic acid" because claim 1 does not provide adequate antecedent basis, and that claim 3, which depends from claim 2, is indefinite in reciting "the mutant target nucleic acid" because claim 2 does not provide adequate antecedent basis. Claim 2 has been amended to

recite "the mutant target nucleic acid" thus properly depending from claim 1 and providing antecedent basis for claim 3. As such, it is respectfully requested that this rejection be removed.

It is also stated in the Office Action that claim 21, which depends from claim 20, is indefinite in reciting "the mutant nucleic acid" because claim 20 does not provide adequate antecedent basis. Claim 21 has been amended to recite "the mutant target nucleic acid" thus properly depending from claim 21. As such, it is respectfully requested that this rejection be removed.

In summary, claims 2 and 21 have been amended to correct informalities in the claim language. As such, it is submitted that the claimed subject matter is clearly defined and, therefore, respectfully requested that the rejections under 35 U.S.C. § 112, second paragraph, be removed.

C. Prior Art Rejections

The rejection of claims 1 to 8, 10, 12, 14 to 16, 18 and 19 under 35 U.S.C. § 102(a) as allegedly anticipated by Nees et al. is respectfully traversed.

It is stated in the Office Action that Nees et al. describe methods for detecting p53 mutations in tumor, tumor-adjacent tissue, and tumor-distant specimens of head and neck cancer patients, and that the tumor-adjacent and tumor-distant specimens did not exhibit a neoplastic morphology. Applicant points out, however, that the claims as amended recite to specific mutant target nucleic acids and target neoplastic nucleic acids, none of which is p53. Nees et al. do not teach or suggest a target nucleic acid other than p53 and, therefore, do not anticipate the claimed invention. Accordingly, it is respectfully requested that the rejection of the claims under 35 U.S.C. § 102(a) as anticipated by Nees et al. be removed.

The rejection of claim 13 under 35 U.S.C. § 102(a) as allegedly anticipated by Nees et al. in view of Sobol et al. is respectfully traversed.

Nees et al. is applied as discussed above. Sobol et al. is applied as evidence that it is inherent that PCR is sufficiently sensitive to detect a target nucleic acid in 1 of 10,000 cells. As discussed above, however, the deficiency of Nees et al. is that the reference does not teach or suggest a target nucleic acid as recited in the claims. Sobol et al. similarly do not teach or suggest such target nucleic acids and, therefore, do not provide the teaching missing in the Nees et al. reference. Accordingly, it is submitted that claim 13 is not anticipated by the cited references, either alone or in combination, and, therefore, respectfully requested that the rejection of claim 13 under 35 U.S.C. § 102(a) as anticipated by Nees et al. in view of Sobol et al. be removed.

The rejection of claim 9 under 35 U.S.C. § 103(a) as allegedly obvious over Nees et al. in view of Watling et al. is respectfully traversed.

Nees et al. is applied as described above. Watling et al. is provided as teaching that p53 is not over-expressed in benign neoplasms. It is alleged in the Office Action that it would have been obvious to one of ordinary skill in the art, viewing the Nees et al. and Watling et al. references, to examine benign neoplasms for p53 expression, for example, to establish a rapid method for detecting or differentiating malignant from benign neoplasms. Applicant submits, however, that previously pending claim 9, which included p53 as a target nucleic acid, was directed to detecting a mutant target p53 as an indication of a benign neoplasm. Watling et al. teach away from such a method because the reference teaches that p53 is not over-expressed in benign neoplasms.

Nevertheless, as discussed above, the amended claims no longer encompass p53 and Watling et al. do not teach or suggest a target nucleic acid as recited in the claims. As such, Watling et al. do not provide the teaching missing in the Nees et al. reference. Accordingly, it is submitted that claim 9 would not have been obvious in view of the cited references, either alone

or in combination, and, therefore, respectfully requested that the rejection of claim 9 under 35 U.S.C. § 103(a) as obvious over Nees et al. in view of Watling et al. be removed.

The rejection of claim 11 under 35 U.S.C. § 103(a) as allegedly obvious over Nees et al. in view of Mullis et al. is respectfully traversed.

Nees et al. is applied as discussed above. Mullis et al. is applied as teaching that cloning of an amplification product allows one to rapidly sequence or express the molecule of interest. As discussed above, Nees et al. describe only analyzing p53, but do not teach or suggest a target nucleic acid as recited in the amended claims. Similarly, Mullis et al. do not teach or suggest a target nucleic acid as recited in the claims and, therefore, do not provide the teaching missing in the Nees et al. reference. Accordingly, it is submitted that claim 11 would not have been obvious in view of the cited references, either alone or in combination, and, therefore, respectfully requested that the rejection of claim 11 under 35 U.S.C. § 103(a) as obvious over Nees et al. in view of Mullis et al. be removed.

The rejection of claims 20 to 27 under 35 U.S.C. § 103(a) as allegedly obvious over Nees et al. in view of Sobol et al. is respectfully traversed.

Nees et al. is applied as discussed above. Sobol et al. is applied as describing methods for detecting carcinoma metastases by detecting a "carcinoma associated sequence." Applicant submits, however, that a "carcinoma associated sequence" as described by Sobol et al. does not include a target nucleic acid as recited in the amended claims. As such, Sobol et al. do not provide the teaching missing in the Nees et al. reference and, therefore, the claimed invention would not have been obvious over the cited references, either alone or in combination. Accordingly, it is respectfully requested that the rejection of the claims under 35 U.S.C. § 103(a) as obvious over Nees et al. in view of Sobol et al. be removed.

The rejection of claim 17 under 35 U.S.C. § 103(a) as allegedly obvious over Nees et al. in view of Knudson et al. is respectfully traversed.

Nees et al. is applied as discussed above. Knudson is provided as teaching that head and neck tumors may contain other mutated oncogenes. However, Knudson does not teach or suggest the target nucleic acid molecules recited as recited in the claims and, therefore, does not provide the teaching missing in the Nees et al. reference. As such, it is submitted that the claimed invention would not have been obvious over the cited references, either alone or in combination and, therefore, respectfully requested that the rejection of claim 17 under 35 U.S.C. § 103(a) as obvious over Nees et al. in view of Knudson et al. be removed.

D. Double Patenting Rejection

The rejection of claims 1 to 27 under the judicially created doctrine of obviousness-type double patenting over claims 1 to 4 of U.S. Patent No. 6,025,127 is respectfully traversed.

A Terminal Disclaimer, disclaiming the term of a patent issuing from the subject application that may extend beyond the term of commonly owned U.S. Patent No. 6,025,127 has been submitted herewith. Accordingly, it is respectfully requested that the rejection of the claims for obviousness-type double patenting be removed.

In view of the amendments and the above remarks, it is submitted that the claims are in condition for allowance, and a notice to that effect is respectfully requested. The Examiner is invited to contact Applicant's undersigned representative if there are any questions relating to the subject application.

Please charge any additional fees, or made any credits, to Deposit Account No. 50-1355.

Respectfully submitted,

Date: November 12, 2002

Richard J. Imbra
Registration No. 37,643
Telephone: (858) 677-1496
Facsimile: (858) 677-1465

USPTO CUSTOMER NUMBER 28213
GRAY CARY WARE & FREIDENRICH LLP
4365 Executive Drive, Suite 1100
San Diego, California 92121-2133

In re Application of
David Sidransky
U.S. Serial No.: 09/420,433
Filed: October 12, 1999
Exhibit A

PATENT
Attorney Docket No.: JHU1180-1

EXHIBIT A

MARKED VERSION OF CLAIMS SHOWING AMENDMENTS

Claims 1, 2, 12, 18 to 21, and 25 were amended as follows:

1. (Thrice amended) A method for detecting the presence of a mammalian mutant target nucleic acid which contributes to the etiology of a neoplasm, in a tumor margin tissue specimen, wherein the specimen is external to a primary neoplasm and the specimen does not exhibit morphological characteristics indicative of neoplastic pathology, and the mutant target nucleic acid is present in the primary neoplasm and the specimen, the method comprising extracting nucleic acid present in the specimen and detecting the presence of the mutant target nucleic acid, wherein the mutant target nucleic acid is selected from APC, DCC, NF1, NF2, RET, VHL, and WT-1.

2. (Thrice amended) The method of claim 1, further comprising, prior to detecting the presence of the mutant target nucleic acid, amplifying the nucleic acid present in the specimen to produce an amplified nucleic acid, wherein said detecting comprises detecting the presence of the mutant target nucleic acid in the amplified nucleic acid.

12. (Thrice amended) A method for detecting metastases in a subject having an excised tumor, the method comprising:

a) isolating tissue from a surgical margin adjacent to the excised tumor;

b) applying to said tissue an oligonucleotide that specifically hybridizes to a neoplastic nucleic acid having a mutant nucleotide sequence, wherein the neoplastic nucleic acid is selected from APC, DCC, NF1, NF2, RET, VHL, and WT-1; and

c) detecting the presence of said neoplastic nucleic acid, wherein the presence of said neoplastic nucleic acid indicates metastases.

18. (Amended) A method for detecting a mammalian target neoplastic nucleic acid having a mutant nucleotide sequence in a tissue specimen which is external to a primary neoplasm, comprising extracting nucleic acid present in the specimen to obtain extracted nucleic acid, and detecting the presence of the target neoplastic nucleic acid in the extracted nucleic acid, wherein the target neoplastic nucleic acid is selected from APC, DCC, NF1, NF2, RET, VHL, and WT-1.

19. (Amended) A method for detecting a mammalian target neoplastic nucleic acid having a mutant nucleotide sequence in a tumor margin tissue specimen which is external to a primary neoplasm, comprising extracting nucleic acid present in the specimen to obtain extracted nucleic acid, and detecting the presence of the target neoplastic nucleic acid in the extracted nucleic acid, wherein the target neoplastic nucleic acid is selected from APC, DCC, NF1, NF2, RET, VHL, and WT-1.

20. (Amended) A method for detecting the presence of a mammalian mutant target nucleic acid which contributes to the etiology of a neoplasm, in a lymph node tissue specimen, wherein the specimen is external to a primary neoplasm and the specimen does not exhibit morphological characteristics indicative of neoplastic pathology, and the mutant target nucleic acid is present in the primary neoplasm and the specimen, the method comprising extracting nucleic acid present in the specimen and detecting the presence of the mutant target nucleic acid, wherein the mutant target nucleic acid is selected from APC, DCC, NF1, NF2, RET, VHL, and WT-1.

21. (Amended) The method of claim 20, further comprising, prior to detecting the presence of the mutant target nucleic acid, amplifying the nucleic acid present in the specimen to produce an amplified nucleic acid, wherein said detecting comprises detecting the presence of the mutant target nucleic acid in the amplified nucleic acid.

25. (Amended) A method for detecting metastases in a subject having an excised tumor, the method comprising:

a) isolating tissue from a lymph node, which is external to a primary neoplasm and does not exhibit morphological characteristics indicative of neoplastic pathology;

b) applying to said tissue an oligonucleotide that specifically hybridizes to a neoplastic nucleic acid having a mutant nucleotide sequence, wherein the neoplastic nucleic acid is selected from APC, DCC, NF1, NF2, RET, VHL, and WT-1; and

c) detecting the presence of said neoplastic nucleic acid, wherein the presence of said neoplastic nucleic acid indicates metastases.